

^{11}C -Choline PET/CT in the Management of Primary Hyperparathyroidism

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Abstract

Primary hyperparathyroidism (PHPT) is a relative common medical problem caused by the inappropriate secretion of parathyroid hormone (PTH) by one or more parathyroid glands. The diagnosis is established by serum calcium and PTH levels and once the diagnosis is established imaging studies help localize the hyperfunctioning adenoma in preparation for curative surgery. Until now, the imaging studies most commonly utilized in PHPT are ultrasonography and $^{99\text{m}}\text{Tc}$ -Sesta-methoxyisobutylisonitrile (MIBI) parathyroid scintigraphy. However, these studies often fail to localize the adenoma and inappropriately delay patient referral to a potentially curative surgery. We present the case of a 64-year-old female with symptomatic PHPT who had 3 negative $^{99\text{m}}\text{Tc}$ -Sestamibi Scans over a period of 5 years who eventually had a PET/CT with ^{11}C -Choline that identified a right lower parathyroid adenoma. She underwent a right lower parathyroidectomy and had a successful outcome. We present a review the current imaging techniques used in the management of PHPT including $^{99\text{m}}\text{Tc}$ -Sesta-MIBI scintigraphy and its limitations and novel use of PET/CT with ^{11}C -Choline and ^{18}F -Choline in this disease and emphasize the fact that, according to current guidelines, failure to localize the adenoma should not delay referral for curative surgery.

Keywords

Primary Hyperparathyroidism, Evaluation of Primary Hyperparathyroidism, ^{11}C -Choline, ^{18}F -Fluorocholine, PET/CT, Treatment of Primary Hyperparathyroidism

1. Introduction

We present the case of a 64-year-old female with a personal history of melanoma in situ. At age 56 a screening bone scan identified osteoporosis. Laboratory studies showed a PTH level of 75.5 pg/ml (nl 7.5 - 53.3 pg/mL) inappropriately high for a serum calcium of 9.7 mg/dl (nl 8.4 - 10.2). Her 25-OH D Vitamin levels were normal at 37 ng/ml (nl 30 - 100), and 24 hr urine calcium was normal 334.4 mg/24 hs (nl > 200). She was referred to an endocrinologist who established the diagnosis of PHPT. A cervical US identified slightly enlarged parathyroid glands (6 mm) at the right superior and right inferior locations, nevertheless a ^{99m}Tc -Sestamibi scan failed to identify an adenoma. She was not referred for surgery. Over the course of the following 4 years she underwent multiple laboratory studies confirming the diagnosis of PHPT. Her PTH levels gradually rose from 75.4 to 98.7 to 105.6 to 164.0 to 187.3 mg/dl. During this time frame she received treatment with calcium, tibolone, vitamin D supplements, and underwent 2 additional ^{99m}Tc -Sestamibi scans that failed to identify a parathyroid adenoma. Clinically, she developed fatigue, difficult concentration, gastritis, and abdominal pain that was labeled as irritable bowel syndrome. The osteoporosis progressed according to image evaluation. She was finally referred for a surgical consultation. Laboratory studies again confirmed the PHPT diagnosis. By this time both, the patient and her endocrinologist, were convinced that a localization study was required prior to an operation. Based on recent reports, a PET/CT with ^{11}C -Choline was performed. Images were obtained 23 and 38 minutes after the IV injection of ^{11}C -Choline (740 MBq). This imaging study identified a right inferior parathyroid adenoma (**Figure 1** and **Figure 2**). Surgical exploration was recommended. Using the radio-guided technique, similar to that described by Norman *et al.* [1], the patient was injected IV 5 mCi ^{99m}Tc -labeled Sesta-MIBI one hour prior to the surgical procedure. The patient underwent a radio-guided, minimally invasive cervical exploration through a 2 cm incision. All 4 parathyroid glands were identified. The right lower gland was found to be enlarged and was completely excised.

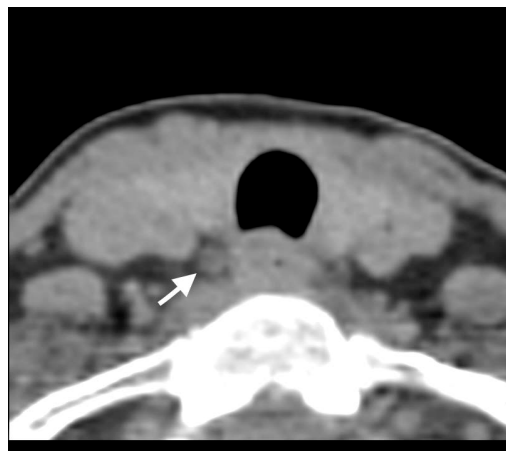


Figure 1. Transaxial CT image of neck showing a nodular lesion behind the lower pole of the right thyroid lobe (arrow).

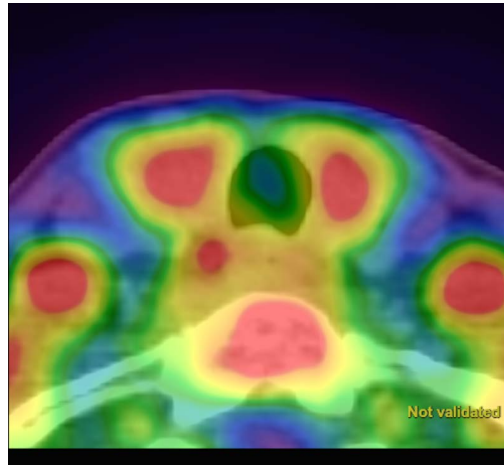


Figure 2. Transaxial ^{11}C -Choline PET/CT fused image of the neck confirming the avidity of the nodule to ^{11}C -Choline, confirming the location of the hyperfunctioning parathyroid adenoma.

Using the gamma probe, this enlarged gland was proven to be hyperactive compatible with a parathyroid adenoma. Using intraoperative PTH levels we confirmed an adequate decrease in the PTH levels, fulfilling the Miami Criteria for cervical exploration for PHPT and confirming the removal of the adenoma causing her PHPT [2]. Her recovery was uneventful, and the patient was discharged to home the following day. The pathology report confirmed a benign parathyroid 12 mm adenoma. At a 6-month follow-up the patient is completely asymptomatic. Her fatigue and abdominal pain have resolved and her calcium, vitamin D, and PTH levels have returned to normal levels. Informed consent was obtained from the patient for this case report.

2. Discussion

Primary hyperparathyroidism (PHPT) is defined as hypercalcemia or widely fluctuating serum calcium levels caused by the inappropriate secretion of parathyroid hormone (PTH) by one or more parathyroid glands [1] [3] [4] [5] [6]. It represents the most common cause of hypercalcemia in the outpatient setting with approximately 1 - 7 cases per 1000 adults [7] [8] [9] [10]. PHPT is caused by the enlargement of a single parathyroid gland or parathyroid adenoma in approximately 75% to 89% of the cases and multiple adenomas or hyperplasia in 15% to 25% of the cases [3] [11] [12] [13] [14].

PHPT is symptomatic in more than 95% of the cases, but symptoms may be subtle [15]. The “classic” pentad of kidney stones, painful bones, abdominal groans, psychic moans, and fatigue overtones is rarely seen today [16] [17] [18]. Nowadays most patients present with subtle symptoms such as fatigue, general malaise, decreased concentration, decreased ability to learn new things, heartburn, arthralgias, myalgias or bone pain [19] [20] [21] [22]. In the past, nephrolithiasis was reported in approximately 40% - 80% of patients, but now occurs only in 20% - 25% of the cases [23] [24].

The diagnosis of PHPT is established by laboratory studies, regardless of the imaging findings [25] [26]. The diagnosis is established by PTH levels that are inappropriately elevated to the patient's serum calcium level. Other adjuncts to confirm the diagnosis include serum calcium, phosphorus (chloride-to-phosphate ratio > 33), and serum 25 OH Vitamin D levels (usually normal or low). In addition, measurement of 24-hour urinary calcium excretion helps exclude familial benign hypocalciuric hypercalcemia as the cause for hypercalcemia [1] [27] [28] [29].

The current management of PHPT consists of surgical excision of the abnormal parathyroid glands as it is the only permanent and curative treatment for the disease. There is growing consensus that surgery is appropriate in the vast majority of patients including those with asymptomatic disease because it is the only definitive therapy and is the only treatment that can prevent the long-term consequences of having the disease [30] [31]. According to American Association of Endocrine Surgeons Guidelines, parathyroidectomy is indicated for all symptomatic patients, and should be considered for most asymptomatic patients as it is more cost-effective than observation or pharmacologic therapy [32]. Surgical exploration for PHPT by an experienced surgical team is associated with a very high cure rate (> 95%) [11]. The operation corrects the symptoms and can have very positive long-term effects in the health of patients preventing morbidity associated with the disease such as osteoporosis, nephrolithiasis, renal failure, cardiovascular disease, and even some malignancies.

3. Imaging Modalities

Once the diagnosis of PHPT has been established via laboratory studies, imaging evaluation helps localize the hyperfunctioning parathyroid gland and thus assists in surgical planning. Parathyroid localization studies are not used to confirm the diagnosis of PHPT, but rather to aid in the surgical management of the disease [33]. Nearly a third of patients with PHPT are not being referred to a surgeon because the endocrinologist has not been able to localize the parathyroid adenoma on a scan [34]. A negative ^{99m}Tc-Sesta-MIBI scintigraphy delays the referral for definitive management of patients with PHPT by an average of 2.7 years [35].

Until now, in our institution, as well as in many institutions worldwide, the imaging study most commonly used to localize the hyperfunctioning parathyroid gland(s) has been the ^{99m}Tc-Sesta-MIBI scintigraphy preferably in combination with hybrid imaging with SPECT/CT (single photon emission computed tomography/computed tomography). This study relies on the fact that both, thyroid and parathyroid tissue demonstrate radionuclide uptake. ^{99m}Tc-Sesta-MIBI washes out of thyroid tissue earlier, leaving only parathyroid tissue that demonstrates activity 2 - 4 hours after injection [36] [37] [38]. MIBI imaging has the advantage over ultrasound in that it is able to identify ectopic parathyroid adenomas. However, the ^{99m}Tc-Sesta-MIBI is negative in more than 35% of patients

with proven PHPT. In some series, the ^{99m}Tc -Sesta-MIBI scintigraphy was negative 65% - 81% of PHPT patients [11] [39]. This high false negative rate of the ^{99m}Tc -Sestamibi scan has prompted the search for other localization imaging techniques for patients with PHPT.

Ultrasonography (US) is one of the modalities that is being used more frequently to localize abnormal parathyroid glands [40]. It is simple, safe, fast, non-invasive, low-cost, not associated with body irradiation, and widely available [4] [41] [42] [43]. In addition, ultrasonography offers the advantage of depicting potential concomitant thyroid disease which is present in approximately 40% of patients with parathyroid disease [44]. Studies of physician-performed ultrasounds show accuracy rates that compare favorably with the accuracy of traditional radiology departments in the vicinity of 75% to 80% [45] [46] [47]. On US, adenomas appear as well-defined hypoechoic lesions with potential cystic or necrotic areas [4] [42]. Neck ultrasound's sensitivity for localizing parathyroid adenoma varies from 57% to 89%. When compared side-by-side to ^{99m}Tc -Sesta-MIBI scintigraphy in patients with overt PHPT, the sensitivity of US was of 90% compared to 70% for ^{99m}Tc -Sesta-MIBI scan [43]. However, in patients with normocalcemic PHPT the sensitivity for both studies decreases to 50% and 40% respectively [26].

Computed tomography scanning (CT) has also been used by some centers to help localize abnormal parathyroid glands. Classic CT scanning has a very low sensitivity, but CT scanning with dynamic contrast images (4D-CT) have shown promising results, with accuracy rates of approximately 88% [48] [49].

Contrast enhanced MRI is a non-invasive, non-radiating imaging technique that can be used when radiation is contraindicated. MRI does not usually play a significant role in PHPT imaging. The sensitivity of MRI is in the range of 80% and is associated with a greater financial cost compared to other imaging modalities such as US. MRI is contraindicated patients with renal failure when gadolinium contrast is necessary and is also contraindicated patients with pacemakers [4] [43] [50] [51].

Recently, PET/CT with ^{18}F -Fluorocholine has been described as a novel imaging modality to help localize the parathyroid adenoma in PHPT. The radiotracer ^{18}F -Fluorocholine integrates into the structure of the cell membrane in proliferating cells. Benign parathyroid adenomas (and carcinomas) show a high membrane turnover because of increased phospholipid-dependent choline kinase activity and this translates into an increased uptake of ^{18}F -Fluorocholine [41] [52]. Thus, PET/CT with ^{18}F -Fluorocholine has the ability to detect not only parathyroid adenomas measuring less than 1cm, but also carcinomas, multiple adenomas, and even gland hyperplasia in patients with secondary hyperparathyroidism. The tracer ^{18}F -Fluorocholine (5 to 10 mCi) is usually injected intravenously and the scan is acquired after 5 - 15 minutes. ^{18}F -Fluorocholine is a positron emitter with half-life of 109.7 minutes and E_{max} of 1.656 MeV; it is cleared via the kidneys and excreted in the urine [53] [54].

When compared to ^{99m}Tc -Sesta-MIBI imaging, PET/CT with ^{18}F -Fluorocholine has shown improved spatial resolution allowing for detection of smaller lesions. In contrast to what occurs with ^{99m}Tc -Sesta-MIBI, PET/CT with ^{18}F -Fluorocholine has proven to be able to detect hyperfunctioning parathyroid adenomas in normocalcemic PHTP as in overt PHPT [55]. In addition, because of the rapid bio-kinetics of choline, it is associated with a shorter study protocol. ^{18}F -Fluorocholine has added advantage of being widely available in many nuclear medicine departments due to its original use for prostate cancer [26] [52]. ^{18}F -Fluorocholine PET/CT is reported to have a sensitivity of 92% and specificity of 100%, in contrast to 49% and 100% for Sesta-MIBI SPECT/CT, 46% and 100% for ^{99m}Tc -Sestamibi/pertechnetate subtraction imaging (with planar images), and 44% and 100% for (99m)Tc-, (99 m) and ^{99m}Tc -Sestamibi dual-phase imaging, respectively. In addition, the acquisition time also compares favorably for ^{18}F -Fluorocholine PET/CT compared to other nuclear medicine modalities (5 - 15 minutes vs. 60 - 64 minutes post-injection) [56]. For all these reasons, many authors consider that PET/CT with ^{18}F -Fluorocholine should now be considered as the new first line imaging technique for patients the PHPT [26]. It offers a sensitive, fast, easy-to-perform imaging modality that is especially useful in the early stages of the disease when the abnormal parathyroid glands are still small and for those cases where ultrasonography, ^{99m}Tc -Sesta-MIBI scintigraphy with planar or SPECT/CT images could not detect the location of the adenoma [52]. In a comparative study of 34 patients with PHPT by Bossert *et al.*; ^{99m}Tc -Sestamibi detected only 15% of abnormal parathyroid glands, US detected 68%, and ^{18}F -Fluorocholine PET/CT detected 71% [26].

In addition to ^{18}F -Fluorocholine, there are other radiotracers which have been studied for the detection of adenomas using the PET/CT technology in patients with PHPT. Such tracers include ^{11}C -Choline, ^{11}C -Methionine, ^{18}F -Fluorodeoxyglucose, and ^{18}F -FET [53].

Similar to ^{18}F -Fluorocholine, ^{11}C -Choline is a precursor of phosphatidylcholine, a phospholipid component of the cellular membrane that is avidly taken up by hyperfunctioning parathyroid cells as well as certain neoplastic cells. In a prospective study of 40 patients, the utility of ^{11}C -Choline PET/CT was compared to that of ^{99m}Tc -Sesta-MIBI imaging. Patients were injected 10 - 20 mCi (370 - 740 MBq) of ^{11}C -Choline and a CT was obtained followed by a PET acquisition initiated approximately 5 minutes after injection. The ^{11}C -Choline PET/CT was positive in 37 of 40 patients. In 29 of 40 cases, ^{11}C -Choline PET/CT and ^{99m}Tc -Sesta-MIBI were concordant, but ^{11}C -Choline PET/CT findings were clearer in 9 of these 29 studies [5]. Authors concluded that ^{11}C -Choline PET/CT is imaging that combines both functional and anatomical information and is a promising tool for parathyroid adenoma localization with the advantages of superior accuracy, quicker and easier acquisition, and better image quality when compared to ^{99m}Tc -Sesta-MIBI scanning [5]. ^{11}C -Choline PET/CT can be performed for almost all patients, including those with renal failure, pacemakers, claustrophobia,

and those patients who may not be able to undergo MRI [57]. ^{11}C -Choline has a short physical half-life (20.4 minutes) and this fact combined with low-dose CT results in much less radiation exposure than other conventional nuclear techniques and 4D CT [57]. It is worth noting, however, that the short half-life of ^{11}C -Choline has also largely limited its use due to the small number of institutions located near a cyclotron production facility. Some European centers use ^{18}F -Fluorocholine instead of ^{11}C -Choline, which alleviates this issue; however, ^{18}F -Fluorocholine is not FDA approved in the United States, and ^{11}C -Choline is approved for restaging recurrent prostate cancer and is thus more readily available [51]. This is precisely the reason why we decided to use ^{11}C -Choline and not ^{18}F -Fluorocholine as the radiotracer for the PET/CT in this patient.

Another tracer that has been successfully used in PHPT is ^{11}C -Methionin. A meta-analysis performed by Kluijfhout *et al.* that included 327 patients in 24 papers concluded that PET/CT with ^{11}C -Methionin has a reported sensitivity of 77% and a positive predictive value of 98% which compares favorably to other imaging techniques. However, in this study ^{18}F -Fluorocholine had a reported sensitivity ranging from 80% - 100% and PPV 89% - 100% which is even better than that observed with ^{11}C -Methionin [26] [54]. Similar to ^{11}C -Choline, ^{11}C -Methionin also has a short half-life (20 min), which limits its use. Authors of this meta-analysis conclude that ^{11}C -Methionin PET/CT may be considered a reliable second-line imaging modality in PHPT, but that ^{18}F -Fluorocholine PET may be associated with a slightly higher accuracy [54]. Martinez-Rodriguez *et al.* and Rosiek *et al.* also consider ^{11}C -Methionin PET/CT to be a helpful strong second-line imaging study to be used when planning for parathyroidectomy. Authors in both of these publications emphasize the usefulness of ^{11}C -Methionine specially in patients in whom their first line imaging techniques of either cervical ultrasonography and/or $^{99\text{m}}\text{Tc}$ -Sesta-MIBI have failed to localize the adenoma [36] [58].

The case presented illustrates the utility of the novel ^{11}C -Choline PET/CT over the traditional Sesta-MIBI scintigraphy for localizing the hyperfunctioning parathyroid adenoma in PHPT. Using the appropriate radiotracers, PET/CT provides better spatial resolution and shorter time acquisition when compared to the traditional $^{99\text{m}}\text{Tc}$ -Sesta-MIBI imaging in patients with PHPT. This higher resolution allows the detection of even the smallest of pathological glands and reduces the duration of the surgery, thus potentially decreasing healthcare costs [36] [58] [59] [60]. The earlier use of this novel imaging modality would have led this patient more promptly to curative surgery.

4. Conclusion

Several imaging studies are now available to localize parathyroid adenomas in PHPT. When selecting an imaging study for this purpose, several factors need to be taken into consideration. These factors include availability, cost, institutional experience with the specific technique, as well as sensitivity, specificity, positive

predictive value of each imaging modality. Based on the data gathered in this review, we conclude that in patients with PHPT, a PET/CT with ¹⁸F-Fluorocholine or ¹¹C-Choline could now be used as a first-line imaging study to localize parathyroid adenomas and should definitely be performed when other imaging studies such as US or ^{99m}Tc-Sesta-MIBI scintigraphy have failed to localize the adenoma. As the current case exemplifies, performing a PET/CT earlier in the disease course may lead to more promptly to curative surgery.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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